PRODUCT MONOGRAPH

IPRAVENT NASAL SPRAY

Ipratropium Bromide Nasal Spray

0.03% and 0.06%

Topical Anticholinergic

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PRODUCT MONOGRAPH

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Ipratropium Bromide Nasal Spray
0.03% and 0.06%

THERAPEUTIC CLASSIFICATION

Topical Anticholinergic

ACTIONS AND CLINICAL PHARMACOLOGY

Ipratropium bromide, a quaternary ammonium derivative of atropine, is an anticholinergic drug. Ipratropium bromide administered intranasally has a localized parasympathetic blocking action which reduces watery hypersecretion from mucosal glands in the nose.

Two nasal provocation trials in perennial rhinitis patients (n=44) using ipratropium bromide nasal spray showed a dose-dependent increase in inhibition of methacholine-induced nasal secretion with an onset of action within 15 minutes. The duration of action of ipratropium bromide nasal spray was also dose-dependent.

Ipratropium bromide administration via nasal aerosol had no marked effect on sense of smell, nasal mucociliary transport, ciliary beat frequency or the air-conditioning capacity of the nose.

Ipratropium bromide is not readily absorbed into the systemic circulation from the nasal mucosa as confirmed by blood level measurements and renal excretion studies with ipratropium nasal spray 0.03%, 0.06% and 0.12%. The plasma half-life in man is less than 2 hours after i.v. administration of ipratropium bromide. Serum protein binding is less than 20%. In placebo-controlled pharmacokinetic trials in a total of 17 volunteers, 0.03%, 0.06%, and 0.12% concentrations of ipratropium bromide nasal spray exhibited linear kinetics up to a total dose of 336 mcg. One clinical trial has shown that the rate of ipratropium absorption was accelerated in a limited number of perennial rhinitis patients (n=4) using ipratropium bromide nasal spray 0.06% chronically versus normal patients (cross trial comparison). This is presumably due to an inflamed

nasal mucosa which is, therefore, more permeable. However, the extent of absorption was the same for patients and normal volunteer groups. Since there was no increase in the frequency of systemic adverse events, the clinical significance of this increased rate of absorption is not known.

Studies in rats have shown that ipratropium bromide does not cross the blood-brain barrier.

In double-blind, placebo-controlled, crossover, single dose pharmacokinetic trials (n=17), ipratropium bromide nasal spray 0.03%, 0.06% and 0.12% (84 mcg, 168 mcg and 336 mcg total nasal dose, respectively) did not significantly affect pupillary diameter, or have any systemic anticholinergic physiologic effect (i.e., changes in heart rate or systolic/diastolic blood pressure) or adverse events (e.g., dry mouth, blurred vision, constipation, difficulty urinating, etc.).

INDICATIONS AND CLINICAL USE

IPRAVENT NASAL SPRAY (Ipratropium Bromide Nasal Spray), 0.03%
For the symptomatic relief of rhinorrhea associated with allergic or nonallergic perennial rhinitis.

IPRAVENT NASAL SPRAY (Ipratropium Bromide Nasal Spray), 0.06%
For the symptomatic relief of rhinorrhea associated with the common cold.

CONTRAINDICATIONS

Known hypersensitivity to ipratropium bromide, atropinics or to any of the ingredients of the ipratropium bromide nasal spray (see COMPOSITION).

WARNINGS

Care should be taken to ensure that ipratropium bromide nasal spray does not reach the eye. There have been isolated reports of ocular complications (i.e., mydriasis, increased intraocular pressure, angle-closure glaucoma and eye pain) when aerosolized ipratropium bromide has been released into the eyes.

Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival and corneal congestion may be signs of acute angle-closure glaucoma. Should any combinations of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately.

Patients must be instructed in the correct administration of ipratropium bromide nasal spray. Care must be taken not to allow the aqueous spray into the eyes. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.

Patients with cystic fibrosis may be more prone to gastrointestinal motility disturbances.

PRECAUTIONS

Caution should be taken to avoid accidental release of the nasal spray into the eyes. Patients with or predisposed to narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction should use ipratropium bromide nasal spray with caution.

Pregnancy

The safety of ipratropium bromide nasal spray administration during pregnancy has not yet been established. The benefits of using ipratropium bromide nasal spray when pregnancy is confirmed or suspected must be weighed against possible hazards to the fetus. Studies in rats, mice and rabbits showed no embryotoxic effects nor teratogenic effects.

Lactation

No specific studies have been conducted on excretion of ipratropium bromide in breast milk. Benefits of ipratropium bromide nasal spray use during lactation should therefore be weighed against possible effects on the infant.

Use in Children

There is insufficient evidence available at present to recommend ipratropium bromide nasal spray for use in children under 12 years of age.

Drug Interactions

If patients are receiving other anticholinergic drugs, including ipratropium containing aerosols for oral inhalation, ipratropium bromide nasal spray should be used with caution because of possible additive effects.

Although the open-label, long-term studies to date have not shown a drug-drug interaction, ipratropium bromide nasal spray should be used with caution in patients concomitantly using intranasal steroids because of the possible adverse local effects (e.g., epistaxis, etc.). Any patient who experiences the above adverse effect should contact their doctor and a reduction in dose or frequency of ipratropium bromide nasal spray or the nasal steroid should be considered.

ADVERSE REACTIONS

Ipratropium Bromide Nasal Spray 0.03%

Adverse reaction information concerning ipratropium bromide nasal spray 0.03% in patients with perennial rhinitis is derived from 5 multicentre, placebo-controlled clinical trials involving 854 patients (454 patients on ipratropium bromide nasal spray and 400 patients on placebo), and a 1-year open-label, follow-up trial. In 3 of the placebo-controlled trials, patients received ipratropium bromide nasal spray, 42 mcg per nostril, or placebo 3 times daily, for 8 weeks. In the other two placebo-controlled trials, ipratropium bromide nasal spray, 21 or 42 mcg per nostril, was administered to patients 2 or 3 times daily for 4 weeks. Of the 285 patients who entered the open-label, follow-up trials, 232 were treated for 3 months, 200 for 6 months, and 159 up to 1 year, with the majority (>86%) of patients going 1 year being maintained on 42 mcg per nostril, 2 or 3 times daily, of ipratropium bromide nasal spray.

Adverse reactions reported for patients who received ipratropium bromide nasal spray 0.03% (42 mcg per nostril), or placebo 2 or 3 times daily, where the prevalence in the ipratropium bromide nasal spray group is 2% or greater and exceeds the prevalence in placebo group, appear in Table 1.

Adverse reactions were usually mild to moderate and transient in the 5 placebo-controlled trials, resulting in discontinuation of treatment for 5.3% of the ipratropium bromide nasal spray 0.03% and 5.3% of the placebo-treated patients. There was no evidence of nasal rebound (i.e., a clinically significant increase in rhinorrhea, posterior nasal drip, sneezing or nasal congestion

severity compared to baseline) upon discontinuation of double-blind therapy in these trials. There were no drug-related serious or anticholinergic adverse events (with the exception of dry mouth reported for 1% of the ipratropium bromide nasal spray and 0.5% of the placebo-treated patients) during the placebo-controlled trials or the 1-year, open-label, follow-up trial in patients on ipratropium bromide nasal spray 0.03%.

Table 1: Adverse Reactions Associated with 0.03% Spray

	% of Patients Reporting Reactions[a]			
	Ipratropium Bromide Nasal Spray 0.03% (n=356)		Placebo Spray (n=347)	
	Incidence %	Discontinued %	Incidence %	Discontinued %
Headache	9.8	0.6	9.2	0
Upper Respiratory Tract Infection	9.8	1.4	7.2	1.4
Epistaxis	9.0	0.3	4.6	0.3
Rhinitis[b]				
Nasal Dryness	5.1	0	0.9	0.3
Nasal Irritation[c]	2.0	0	1.7	0.6
Other Nasal Symptoms[d]	3.1	1.1	1.7	0.3
Pharyngitis	8.1	0.3	4.6	0
Nausea	2.2	0.3	0.9	0

[a]This table includes only adverse reactions for which the prevalence in the ipratropium bromide nasal spray group was 2%or greater and exceeds the prevalence in the placebo group.
[b]All reactions are listed by their WHO term; rhinitis has been presented by descriptive terms for clarification.
[c]Nasal irritation includes reports of nasal itching, nasal burning, nasal irritation and rhinitis ulcerative.
[d]Other nasal symptoms include reports of nasal congestion, increased rhinorrhea, increased rhinitis, posterior nasal drip, sneezing, nasal polyps and nasal edema.

Nasal adverse events and adverse reactions were reported for 84 (29.5%) of the 285 patients in the 1-year open-label, follow-up trial. The incidence for the most frequently reported nasal adverse reactions were nasal congestion (1.4%), nasal dryness (9.5%), and epistaxis (4.2%).

Drug-related and non-drug related nasal dryness and/or epistaxis occurred in 45 patients. It resolved with continued treatment or dose reduction in 40 of these patients (89%), and required discontinuation of treatment in 5 patients (11%).

Adverse reactions, which were found in less than 2% of perennial rhinitis patients receiving ipratropium bromide nasal spray 0.03% in the 5 multi-centre, placebo-controlled clinical trials and 1-year open-label follow-up trial were: rash, urticaria and conjunctivitis.

Adverse events, observed in perennial rhinitis patients receiving ipratropium bromide nasal spray 0.03% in the 5 multicentre, placebo-controlled clinical trials and 1-year open-label follow-up trials were: paresthesia, fatigue, dizziness, insomnia, dysphonia, migraine, vertigo, furunculosis, generalized edema, diarrhea, abdominal pain, taste perversion and xerophthalmia.

There have been isolated reports of ocular events such as mydriasis, increased intraocular pressure, glaucoma and eye pain associated with the release of aerosolized ipratropium into the eyes. These ocular events have not been reported with the use of ipratropium nasal spray.

Ipratropium Bromide Nasal Spray 0.06%

Adverse reaction information concerning ipratropium bromide nasal spray 0.06% in patients with the common cold is derived from 2 multicentre, placebo-controlled clinical trials involving 1276 patients (195 patients on ipratropium bromide nasal spray 0.03%, 352 patients on ipratropium bromide nasal spray 0.06%, 189 patients on ipratropium bromide nasal spray 0.12%, 351 patients on placebo and 189 patients receiving no treatment). The adverse reactions reported for patients receiving ipratropium bromide nasal spray 0.06% administered 3 or 4 times daily, where the incidence in the ipratropium bromide nasal spray group is 1% or greater and exceeds the prevalence in the placebo group, appear in Table 2.

Table 2: Adverse Reactions Associated with 0.06% Spray

	% of Patients Reporting Reactions*	
	Ipratropium Bromide Nasal Spray 0.06% (n=352)	**Placebo (n=351)**
Epistaxis or Nosebleed	5.4	1.4
Nasal Dryness	4.8	2.8
Blood-tinged Nasal Mucus	2.8	0.9
Dry Mouth/Throat	1.4	0.3
Nasal Congestion	1.1	0.0

*This table includes only those adverse reactions for which the frequency in the ipratropium bromide nasal spray group was 1% or greater and exceeds the frequency in the placebo group.

Adverse reactions reported in less than 1% of patients with the common cold receiving ipratropium bromide nasal spray 0.06% in 2 multicentre, placebo-controlled clinical trials were: tachycardia, conjunctivitis and abnormal vision.

Adverse events seen in the same population include paresthesia, dizziness, dysphonia and taste perversion.

Ipratropium bromide nasal spray 0.06% was well tolerated by the patients, with the most frequently reported adverse reactions being minor local nasal reactions. The majority of the adverse reactions were mild to moderate in nature, none were considered serious, none resulted in hospitalization and no patient receiving ipratropium bromide nasal spray 0.06% was discontinued from the trial due to an adverse reaction. There was no evidence of rebound of nasal symptoms.

There have been isolated reports of ocular events such as mydriasis, increased intraocular pressure, glaucoma and eye pain associated with the release of aerosolized ipratropium bromide into the eyes. These ocular events have not been reported with the use of ipratropium bromide nasal spray.

Postmarketing Experience

Worldwide safety data, which includes postmarketing data, spontaneous reports, literature reports, and clinical trial reports, indicate that the most frequent undesirable effects of ipratropium bromide nasal spray are local nasal reactions such as epistaxis, dryness of the nose and nasal irritation, nasal congestion, nasal burning sensation, headache and nausea.

Anticholinergic side effects such as tachycardia and palpitations, dryness of mouth/throat, ocular accommodation disturbances, gastrointestinal motility disturbances and urinary retention are rare and reversible.

Allergic-type reactions such as skin rash, angioedema of tongue, lips and face, urticaria, laryngospasm and anaphylactic reactions may occur.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute overdosage by intranasal administration is unlikely since ipratropium bromide is not well absorbed systemically after intranasal or oral administration. Minor systemic manifestation of anticholinergic action, including dry mouth, visual accommodation disturbances and increased heart rate may occur.

Should signs of serious anticholinergic toxicity appear, cholinesterase inhibitors may be considered.

DOSAGE AND ADMINISTRATION

The dose of IPRAVENT NASAL SPRAY (Ipratropium Bromide Nasal Spray) 0.03% for symptomatic relief of rhinorrhea associated with allergic or nonallergic perennial rhinitis is 2 sprays (42 mcg) per nostril 2 or 3 times a day (total dose 168 to 252 mcg/day). Optimum dosage varies with the response of the individual patient.

The dose of IPRAVENT NASAL SPRAY (Ipratropium Bromide Nasal Spray) 0.06% is 2 sprays (84 mcg) per nostril 3 or 4 times daily (total dose 504 to 672 mcg/day) as required for symptomatic relief of rhinorrhea associated with the common cold.

Treatment in the common cold has only been studied up to 4 days. Efficacy and safety of treatment beyond 4 days have not been established, although there has been no evidence of adverse safety effects with longer treatment in perennial rhinitis patients.

Children

Not recommended for use in children under 12 years of age.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

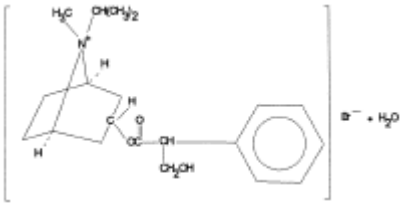
Common Name: Ipratropium bromide

Chemical Name:

1) 8-Azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate (*endo, syn*)- (±)-;

2) (8*r*)-3α-Hydroxy-8-isopropyl-1α$_H$,5α$_H$-tropanium bromide (±)-tropate monohydrate.

Structural Formula:



Molecular Formula: $C_{20}H_{30}BrNO_3 \cdot H_2O$

Molecular Weight: 430.38

Description: Ipratropium bromide is a white or almost white, crystalline powder, soluble in water, freely soluble in methanol, slightly soluble in alcohol.

Melting Point: It melts at about 230°C with decomposition.

Acidity: The pH of a 1% aqueous solution is between 5.0 and 7.5

Optical Rotation: The angle of optical rotation, measured on solution S, is -0.10° to +0.10°.

COMPOSITION

Each spray of IPRAVENT NASAL SPRAY (Ipratropium Bromide Nasal Spray) 0.03% is designed to deliver 0.07 mL which contains: ipratropium bromide 21 µg. Nonmedicinal ingredients: benzalkonium chloride, edetate disodium, hydrochloric acid, purified water, sodium chloride and sodium hydroxide.

Each spray of IPRAVENT NASAL SPRAY (Ipratropium Bromide Nasal Spray) 0.06% is designed to deliver 0.07 mL which contains: ipratropium bromide 42 µg. Nonmedicinal ingredients: benzalkonium chloride, edetate disosdium, hydrochloric acid, purified water, sodium chloride and sodium hydroxide.

STABILITY AND STORAGE RECOMMENDATIONS

Store tightly closed at room temperature 15-30°C (59-86°F). The contents are stable up to the expiration date stamped on the label. Avoid excessive heat or freezing. Keep out of reach of children.

AVAILABILITY OF DOSAGE FORMS

IPRAVENT NASAL SPRAY (Ipratropium Bromide Nasal Spray) 0.03%

Each spray (0.07 mL) contains ipratropium bromide 21 µg. Available in bottles of 30 mL, fitted with a metered nasal spray pump, a safety clip to prevent accidental discharge of the spray and a clear plastic dust cap. The 30 mL bottle is designed to deliver 345 sprays of 0.07 mL each or 28 days of therapy at the maximum recommended dose (2 sprays per nostril 3 times a day).

IPRAVENT NASAL SPRAY (Ipratropium Bromide Nasal Spray) 0.06%

Each spray (0.07 mL) contains ipratropium bromide 42 mcg. Available in bottles of 15 mL, fitted with a metered nasal spray pump, a safety clip to prevent accidental discharge of the spray and a clear plastic dust cap. The 15 mL bottle is designed to deliver 165 sprays of 0.07 mL each or 10 days of therapy at the maximum recommended dose (2 sprays per nostril 4 times a day).

INFORMATION FOR THE PATIENT

IPRAVENT NASAL SPRAY
Ipratropium Bromide Inhalation Solution, 0.03% and 0.06%

READ COMPLETE INSTRUCTIONS CAREFULLY AND USE ONLY AS DIRECTED.

IPRAVENT NASAL SPRAY, 0.03% is used to treat the runny nose associated with perennial allergic or nonallergic rhinitis. IPRAVENT NASAL SPRAY, 0.06% is used to treat the runny nose associated with the common cold. It works to stop the glands in your nose from producing excessive nasal secretions. IPRAVENT NASAL SPRAY must be prescribed by a doctor.

These instructions explain how to use IPRAVENT NASAL SPRAY and how to avoid problems while you are using the product. If you have any questions after reading these instructions, be sure to talk to your doctor or pharmacist.

BEFORE YOU START

Before you start to use IPRAVENT NASAL SPRAY, be sure to tell your doctor if:

· you are pregnant or intend to become pregnant;
· you are breast feeding;

- you have any other health problems, now or in the past;
- you have eye problems, such as predisposition to glaucoma;
- you have difficulty/trouble urinating or problems with your prostate;
- you are taking any other medications including eye drops or any medications you can buy without a prescription;
- you have any allergies or reactions to foods or drugs.

Remember to tell any other doctor, dentist or pharmacist whom you consult with that you are using IPRAVENT NASAL SPRAY.

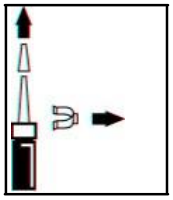
HOW TO USE YOUR IPRAVENT NASAL SPRAY
Do not exceed the number of sprays, or the length of use, prescribed by your doctor.

IPRAVENT NASAL SPRAY has been prescribed to treat <u>your</u> current condition. Do not give it to other people.

Do not take other medication without your doctor's advice.

Keep out of the reach of children.

1) Remove the clear plastic dust cap and the safety clip from the nasal spray pump. The safety clip prevents the accidental discharge of the spray in your pocket or purse.



- 2) The nasal spray pump must be primed before IPRAVENT NASAL SPRAY is used for the first time. To prime the pump, hold the bottle with your thumb at the base and your index and middle fingers on the white shoulder area. Make sure the bottle points upright and away from your eyes. Press your thumb firmly and quickly against the bottle seven times. The pump is now primed and can be used. Your pump should not have to be reprimed unless you have not used the medication for more than 24 hours; repriming the pump will only require one or two sprays.

3) Before using IPRAVENT NASAL SPRAY, blow your nose gently to clear your nostrils, if necessary.

4) Close one nostril by gently placing your finger against the side of your nose, tilt your head slightly forward and, keeping the bottle upright, insert the nasal tip into the other nostril. Point the tip toward the back and outer side of the nose.

5) Press firmly and quickly upwards with the thumb at the base while holding the white shoulder portion of the pump between your index and middle fingers. Following each spray, sniff deeply and breathe out through your mouth.

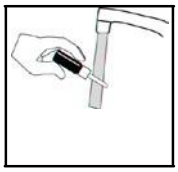
6) After spraying the nostril and removing the unit, tilt your head backwards for a few seconds to let the spray spread over the back of the nose.

7) Repeat steps 4 through 6 in the other nostril.

8) Replace the clear plastic dust cap and safety clip.

9) When the amount of IPRAVENT NASAL SPRAY begins to run low, the amount of medication in each spray cannot be assured. Therefore, at some time before the medication is completely used up, you should consult your physician or pharmacist to determine whether a refill is needed. You should not take extra doses of IPRAVENT NASAL SPRAY without consulting your physician.

TO CLEAN



If the nasal tip becomes clogged, remove the clear plastic dust cap and safety clip. Hold the nasal tip under running, warm tap water for about a minute. Dry the nasal tip, reprime the nasal spray pump (step 2 above), and replace the plastic dust cap and safety clip.

Avoid spraying IPRAVENT NASAL SPRAY in or around your eyes. Should this occur, immediately flush your eyes with cool tap water for several minutes. If you accidentally spray IPRAVENT NASAL SPRAY in your eyes, you may experience a temporary blurring of vision and increased sensitivity to light, which may last a few hours.

Caution for patients using IPRAVENT NASAL SPRAY for chronic nasal inflammation:
IPRAVENT NASAL SPRAY is intended to relieve your rhinorrhea (runny nose) with regular use. It is therefore important that you use IPRAVENT NASAL SPRAY as prescribed by your physician. Some improvement in rhinorrhea is usually apparent during the first full day of treatment with IPRAVENT NASAL SPRAY. However, maximum benefit may not occur for up to several weeks after treatment has started.

OTHER EFFECTS
Like any other drug product, IPRAVENT NASAL SPRAY may cause unwanted effects along with its good effects. If you do experience any of the unwanted effects listed below, you should contact your doctor. He/she may recommend that you lower your dose of IPRAVENT NASAL SPRAY.

- very dry nose
- dry mouth
- nasal irritation
- nose bleeds

If you experience any of the following unwanted effects, contact your doctor right away.

- blurred vision or pain in the eyes
- fast or irregular heart beat
- difficult or painful urination
- skin rash
- increased wheezing or tightness in the chest
- swelling of the tongue or lips
- difficulty in swallowing

Non-medicinal ingredients in IPRAVENT NASAL SPRAY include: benzalkonium chloride, edetate disodium, hydrochloric acid, purified water, sodium chloride and sodium hydroxide.

STORAGE
Store tightly closed at room temperature between 15 - 30°C (59 - 86°F). Avoid excessive heat or freezing. Keep out of reach of children.

PHARMACOLOGY

ANIMAL

In vivo

Ipratropium bromide is an anticholinergic agent which, when delivered by oral inhalation, exerts its effects primarily in the bronchial tree. It abolishes acetylcholine-induced bronchospasm in the guinea pig and dog after intravenous administration at an ED_{50} of 0.15-0.40 mcg/kg with a transient effect on blood pressure. By oral inhalation, approximately 25 mcg of ipratropium bromide produces a 50% inhibition of acetylcholine-induced bronchospasm in the dog with no detectable effect on blood pressure but with an increased duration of action compared to i.v. administration.

The anticholinergic effects of ipratropium bromide were evaluated in several other organ systems following oral, subcutaneous, intravenous and inhalation administration. In dogs, a 50% increase in heart rate resulted from a subcutaneous dose of about 0.011 mg/kg (equipotent to atropine) but the equi-effective oral dose of ipratropium was 58 times greater. When given by oral inhalation, no increase in heart rate or pathological changes in ECG pattern were recorded at doses up to 8 mg. In another experiment, blood pressure and heart rate in the dog could be modulated after i.v. administration of low doses of ipratropium bromide, but metered aerosol administration of 100 puffs (40 mcg/puff) was required to produce an 11% increase in heart rate.

Salivary secretion in rat, mouse and dog was effectively inhibited by low parenteral doses of ipratropium bromide (0.001 to 0.032 mg/kg) but when given by the oral route, the effective dose increased over 100-fold. Aerosol administration in dogs of about 65 puffs (0.04 mg/puff), produced a 50% inhibition of salivary flow. Similarly, effects on gastric secretion in the rat showed at least a 100-fold difference between effective enteral and subcutaneous doses.

Mydriatic effects of ipratropium bromide in mice were approximately equipotent to atropine after s.c. doses but were 10-20 times less after oral administration. Tests of doses of ipratropium bromide up to 100 mg/kg in the rabbit showed no effect on the central nervous system.

Ipratropium bromide, subcutaneously, inhibited the secretory effects of the cholinergic agonist, oxtremorine, in mice. It also exhibited spasmolytic effects equivalent to, or greater than, atropine in isolated guinea pig gut.

In vitro* and *in situ

Tests with the isolated rectum of the guinea pig (*in vitro*) demonstrated the effectiveness of ipratropium bromide in suppressing the spasmogenic effects of acetylcholine and pilocarpine. It was ineffective against histamine or barium chloride-induced spasm. Ipratropium bromide exerted anticholinergic effects on the *in situ* bladder and intestine preparations of the dog. Intravenous doses were 500 times more potent than oral or intraduodenal administration.

HUMAN

Pharmacokinetics

In man, inhalation of 555 mcg of radiolabelled aerosolized ipratropium bromide (about 14 times the recommended therapeutic dose) produced peak plasma levels of 0.06 ng/mL after 3 hours. The plasma concentration-versus-time curve was similar to that seen after oral administration, likely reflecting the large fraction of inhaled dose which is deposited on the pharyngeal mucosae and swallowed. Intravenous administration of 1.0 mg in man showed a rapid distribution into tissues with a disposition half-life (alpha phase) of approximately 5 minutes, and a terminal half-life (beta phase) of 3-4 hours. Plasma concentrations after inhaled ipratropium bromide were about 1000 times lower than equipotent oral or intravenous doses (15 and 0.15 mg, respectively). Up to 8 metabolites of ipratropium bromide have been detected in man, rat and dog. In man, about 70% of the drug is excreted unchanged after i.v. administration and only one metabolite exceeds 10% of the total radioactivity. The elimination occurs primarily via the kidney with less than 10% of the total intravenous dose excreted via the biliary or fecal route. After oral or inhaled doses, however, up to 90% of the dose is detectable in the feces, suggesting poor absorption. Serum protein binding is less than 20%.

Pharmacokinetic studies in healthy volunteers revealed that the local application of Ipratropium Bromide Nasal Spray resulted in very low (<10%) systemic absorption of the compound, based on the assessment of 24 hour ipratropium urine excretion.

In a double-blind, placebo-controlled, induced-cold pharmacokinetic trial in 40 volunteers pre- and post-infection with Human Rhinovirus 39, Ipratropium Bromide Nasal Spray 0.06% (n=22) exhibited similar pharmacokinetic profiles in plasma and urine irrespective of nasal mucosa condition. There was no potentiation of either single or multiple doses in the systemic absorption of ipratropium bromide across inflamed nasal mucosa due to the induced cold compared to the non-inflamed state.

Pharmacodynamics

Methacholine Challenge

It has been established that the topical application of methacholine to the nasal mucosa under controlled clinical conditions can be used to conduct a simple and reproducible test for the measurement of nasal reactivity. Five pharmacodynamic studies on Ipratropium Bromide Nasal Aerosol were conducted using the methacholine test. These studies were designed to determine whether ipratropium bromide, a specific antagonist of methacholine, could effectively and consistently reduce nasal secretions in healthy subjects and in patients with rhinitis. Results from these studies indicated that aerosolized intranasal ipratropium bromide effectively reduces hypersecretion after methacholine challenge, in both healthy subjects and allergic/nonallergic patients. No significant change in the number of sneezes or nasal congestion was found. No local or systemic side effects were reported.

These results are supported by the evidence from a methacholine challenge study performed with Ipratropium Bromide Nasal Spray (aqueous) 0.03% and 0.12% (42 and 168 mcg/nostril, respectively) in patients with perennial rhinitis. Dose-dependent inhibition of the nasal hypersecretion induced by methacholine was observed, with an onset of action within 15 minutes. Duration of action was also dose-dependent, with the lower dose no longer effective after 3 hours, and the higher dose effective for up to 6 hours. Placebo-controlled efficacy trials in patients with perennial rhinitis exhibited a much longer duration of action (up to 12 hours).

Tolerance Studies

The first tolerance study, a randomized, double-blind, three period crossover study, examined the effect of single high doses of aerosolized intranasal ipratropium bromide on healthy subjects. Subjects received single doses of 200 or 400 mcg (10 or 20 puffs altogether) ipratropium bromide or placebo on separate test days. Ten subjective symptoms (general malaise, palpitations, sensation of heat, thirst, speech impediment, blurred vision, dryness of nose, dryness of mouth, headache) were assessed by the individuals, using a visual analogue scale.

The objective measures (blood pressure, pulse rate, nearest reading distance, amount of saliva produced in a 3 minute period) did not reveal any significant differences. No statistically significant differences were found between the 3 treatment groups for any of the subjective parameters.

The second tolerance study was designed to evaluate the effects of single and repeated administration of aerosolized ipratropium bromide to the nasal mucosa. Twelve healthy male subjects were entered into the study. Seven subjects were given a single administration of ipratropium as follows:

2 subjects - 40 mcg/nostril
2 subjects - 80 mcg/nostril
3 subjects - 160 mcg/nostril

Five subjects received multiple administrations as follows:

2 subjects - 40 mcg/nostril qid for 7 days
(Total daily dose - 320 mcg)

3 subjects - 80 mcg/nostril qid for 7 days
(Total daily dose - 640 mcg)

No substantial changes were seen in the results of the physical examination following single or repeated administration. No laboratory values were outside the normal range, with the exception of 1 subject whose WBC increased above the normal range 1 day after administration. Since this subject received the lowest dose (80 mcg) and such an abnormal change was not observed in other subjects receiving higher doses, the change was not judged to be attributable to the drug.

There were no observable changes in the nasal mucosa or nasal secretions. One subject receiving a multiple dose (40 mcg/nostril) reported nasal blockage and another subject, in the same group, a dry nose. Two subjects receiving a single dose of 40 mcg per nostril reported nasal blockage.

A third tolerance study was designed to closely monitor changes in the structure and function of the nose during aerosolized intranasal ipratropium bromide treatment for one year. Biopsy, microscopy and ciliary motility measurements were done at 6 month intervals (0, 6 and 12 months). Olfactory detection thresholds were determined at 0, 3, 6, 9, and 12 months.

Biopsy samples were studied to assess whether the histology of the mucosal layer, or the thickness of the basement membrane, could change during long-term use of ipratropium bromide.

Although there are virtually no >normal= baseline values in this area, it was assumed that any significant trauma could be assessed by studying nasal biopsy samples. Ciliary motility was measured using a sample of mucosal scraping, recorded under a light microscope by a slow motion version of a video.

Twenty patients and seven healthy controls (only 3 controls for the biopsies) were entered into the study. Twelve patients participated for the full year. None of the patients withdrew from the study because of adverse effects. Patients were instructed to use 40 mcg per nostril 4 times a day initially, but were later permitted to tailor the dose to their individual needs.

With regard to most parameters (i.e. leukocytic infiltration, neutrophil polymorphs, lymphocytes, eosinophils, oncocytes, margination of leukocytes, mononuclear cells), between 50 and 100% of the patients= biopsy results remained virtually unchanged. Parameters such as edema and vascular dilatation showed an overall decrease from entry to final assessment. Minimum basement membrane thickness (0 versus 6 and 12 months) comparisons were not significantly different. There was a significant reduction in the maximum thickness at 6 and 12 months compared to baseline. However, according to the lab control data, the basement membrane thickness of the patients in the study was not outside the normal range at any time point.

No significant changes were seen in the structure or function of the nasal cilia, or the sense of smell.

SPECIAL EFFECTS

In vitro and ***in vivo*** studies were conducted to assess the effect of aerosolized intranasal ipratropium bromide on mucociliary transport in healthy subjects.

In vivo

Twelve healthy subjects participated in a randomized, double-blind, crossover trial involving the saccharin transport test. Nasal mucociliary transport time was measured by the saccharin transport time (ST) 15 minutes after each 80 mcg ipratropium bromide or placebo administration. In the test, a 5 mcg granule of saccharin was placed approximately 1 cm into the nostril and the time elapsed until the subject experienced a sweet taste was recorded. A baseline ST was performed prior to dosing on the first day. Each subject received active drug twice and placebo twice, with at least a 48 hour interval between tests.

There were no statistically significant differences between baseline, ipratropium bromide, and the placebo values for the mean saccharin transport time. No local or systemic side effects were reported.

In vitro

A study was conducted to examine the effect of ipratropium bromide on the ciliary beat frequency of the nasal mucosa. Specimens from nine healthy subjects were obtained from the inferior nasal concha with a bronchoscopy brush after thorough cleansing of the nose. Viable cells were perfused with solutions of ipratropium bromide in concentrations varying from 0 to 0.0001 mg/mL.

At baseline, before perfusion, the average ciliary beat frequency was 10.8 ± 1 Hz. There was no significant change in either the beat frequency for the samples perfused with ipratropium bromide, or for those with no perfusion.

Nasal Air Conditioning Capacity

The effect of aerosolized intranasal ipratropium bromide on the air conditioning capacity of the nose was assessed in a study with 16 healthy subjects and 9 patients with vasomotor rhinitis.

Each subject received an assessment for a 10 minute period prior to, and 15 to 30 minutes after the administration of 60 mcg ipratropium bromide to one nostril. The patients were measured twice on two different days. At each measurement, enthalpy (kJ) and the amount of water loss (g) over a 10 minute period were calculated.

There was no significant difference between the results obtained before and after treatment with ipratropium bromide in healthy subjects or in patients with vasomotor rhinitis. It was concluded that ipratropium does not influence air conditioning capacity in patients with vasomotor rhinitis or in healthy volunteers during short-term treatment.

CLINICAL STUDIES

Ipratropium Bromide Nasal Spray 0.03%

In patients with perennial rhinitis (allergic or nonallergic), use of Ipratropium Bromide Nasal Spray 0.03% (42 mcg per nostril, two or three times daily; n=343) resulted in a clinically significant decrease in the severity and duration of rhinorrhea compared to placebo (n=331) in four separate multicenter, parallel group trials. This decrease in rhinorrhea resulted in a substantial reduction in the degree of interference with patient daily activities and moods more consistently in the Ipratropium Bromide

Nasal Spray than placebo treatment groups. A modest decrease in other nasal symptoms (i.e. posterior nasal drip, sneezing and congestion) was also observed in both the Ipratropium Bromide Nasal Spray and placebo treatment groups, and may represent the salutary effect of the nasal spray formulation excipients.

Results from three eight-week, double-blind, placebo-controlled clinical trials (n=580, 295 patients receiving Ipratropium Bromide Nasal Spray 0.03%) have shown that significant symptomatic relief of rhinorrhea was obtained on the first full day of treatment with Ipratropium Bromide Nasal Spray, with continued gradual improvement over the eight-week treatment period. Upon entry into these trials, 20% of patients (n=117) reported lack of control of rhinorrhea with prior use of antihistamines; there was a significant reduction in rhinorrhea in the patient group unresponsive to antihistamines assigned to Ipratropium Bromide Nasal Spray 0.03% (n=61), as well as in patients who had been responsive to antihistamines (n=430).

In a one-year, open-label follow-up trial involving 285 patients with nonallergic perennial rhinitis, daily use of Ipratropium Bromide Nasal Spray 0.03%, 21 or 42 mcg per nostril, two or three times daily, continued to control rhinorrhea and was well tolerated, with no evidence of tachyphylaxis. Patient and physician global assessments demonstrated that long-term treatment may also contribute to the control of posterior nasal drip, sneezing and nasal congestion. In addition, use of concomitant medications (antihistamines, decongestants, and intranasal steroids) for greater than 3 months to treat perennial rhinitis symptoms was decreased from 26% of patients (n=75) prior to the study to 13% (n=37) during long term treatment.

Ipratropium Bromide Nasal Spray 0.06%

In two separate multicenter parallel group trials, involving patients with rhinorrhea associated with the common cold, treatment with Ipratropium Bromide Nasal Spray 0.06% (84 mcg/nostril, administered three to four times daily; n=352) resulted in a significant reduction of rhinorrhea, compared to placebo (n=351). Rhinorrhea was measured by nasal discharge weight as well as the patients= subjective assessment of severity of rhinorrhea using a visual analog scale. A majority of patients receiving Ipratropium Bromide Nasal Spray 0.06% perceived significant improvement in their symptoms of rhinorrhea from moderate or severe at baseline to very mild or no symptoms at all following a single dose.

TOXICOLOGY

ACUTE TOXICITY

SPECIES	SEX	ROUTE	LD_{50} (mg/kg)
Mouse		i.v.	13.5
Mouse	M	i.v.	12.3
Mouse	F	i.v.	15.0
Mouse		s.c.	322.0
Mouse		s.c.	300.0
Mouse		oral	2010.0
Mouse		oral	1038.0
Rat		i.v.	15.8
Rat		s.c.	1500.0
Rat		oral	4000.0
Rat		oral	1722.0

The signs of toxicity were apathy, reduced mobility, ataxia, paralysis of skeletal muscle, clonic convulsions and death from respiratory failure. Toxic signs persisted for 3 hours after i.v. administration and for 8 days after oral administration.

Acute dose tolerance studies were performed in dogs. No deaths occurred up to doses of 400 mg/kg oral or 50 mg/kg subcutaneous. Signs of toxicity were mydriasis, dryness of oral, nasal and optic mucosa, vomiting, ataxia, increased heart rate, decreased body temperature, and death from respiratory failure.

An acute inhalation toxicity study of ipratropium bromide administered as a 4% and 8% solution to guinea pigs was performed. No toxic signs were observed with the 4% solution and death occurred after 5 hours of administration with the 8% solution (approximately 200 mg/kg).

Anesthetized normal and hypoventilated dogs tolerated doses up to 200 puffs (4 mg) of ipratropium bromide without ECG changes or heart failure. Reductions in heart rate were observed. Similar findings were seen in dogs given i.v. infusions (10 mg/kg/min) up to 1550 mg/kg or 1000 mg/kg plus 200 puffs from a placebo inhaler. Blood pressure reductions were also seen in these experiments.

An acute inhalation, dose tolerance study in rats using doses of up to 160 puffs (3.2 mg) from an Ipratropium Bromide inhaler (oral), was performed. No deaths occurred.

SUBACUTE TOXICITY

Oral

A subacute toxicity study of 9 weeks duration in rats utilizing doses of 10, 100 and 500 mg/kg revealed no pathological findings apart from a dose related decrease in food consumption and growth rate.

A 4 week study in dogs using doses of 3, 30 and 150 (for 3 weeks) increased to 300 mg/kg showed mydriasis, inhibition of lacrimal and salivary secretion, tracheal and ocular inflammation, decreased food intake and weight loss at the medium and high doses. Three of 6 dogs died when the dose was increased from 150 to 300 mg/kg.

A supplementary study in dogs of 13 weeks duration, using doses of 1.5, 3.0 and 15 mg/kg revealed no pathological changes apart from a dose related inhibition of lacrimal secretions and associated keratoconjunctivitis and dryness of the mouth.

Subcutaneous

Rats were treated with subcutaneous injections of 1, 10 and 100 mg/kg. One death occurred in the 10 mg/kg dose group from paralytic ileus. Inflammatory changes were noted at the injection site. A 4 week study in dogs using doses of 10, 20 and 30 mg/kg (increased to 40 mg/kg on the last 5 days) was conducted. Dryness of the oral and nasal mucous membranes and mydriasis were noted along with conjunctivitis and keratitis associated with decreased lacrimal secretions. A decrease in food intake and body weight also occurred. One dog died in the high dose group. Signs of liver damage were noted in 2 high dose dogs. Low testicular weights, which have not been observed in other subsequent studies, were also observed.

Inhalation (Oral)

Twelve rats were exposed to aerosolized ipratropium bromide in a concentration of 11.5 mcg/L for 1 hour, 4 times per day for 7 days. No drug toxicity was found.

In another study, administration of ipratropium bromide in doses of 128, 256 and 384 mcg per rat per day for 30 days showed no signs of toxicity apart from a low grade inflammatory response and areas of fibrosis and hemorrhage in the parametrium of 2/9 females in the high dose group. This finding has not been observed in subsequent studies.

Four rhesus monkeys inhaled 500 mcg of ipratropium bromide twice a day (total dose 1 mg/day) for 7 days without the appearance of any drug induced toxicity.

In another study rhesus monkeys were given ipratropium bromide in doses of 200, 400 and 800 mcg/day by inhalation for 6 weeks. Included in the tests were measurements of mucociliary transport rate and ciliary beat frequency. No signs of drug toxicity were found.

CHRONIC

Oral

A 6 month and a 1 year study in rats using doses of 6, 30 and 150 mg/kg were performed. The high dose was increased to 200 mg/kg after 14 weeks. Reductions in food consumption and growth rates were observed in the highest dose group. A dose dependent constipation which caused severe coprostasis and dilation of the intestines was observed in the highest dose groups. A toxic hepatotosis was observed in some animals of the highest dose group.

Ipratropium bromide was administered to dogs in doses of 1.5, 3.0, 15.0 and 75.0 mg/kg for 1 year. A decrease in body weight development was seen in the highest dose group and food consumption was reduced in the dogs receiving 3 mg/kg and above. Emesis was seen in all treated groups. A dose dependent decrease (3 mg/kg and above) in nasal, oral and lacrimal secretions - the latter leading to keratoconjunctivitis - was observed. Increases in SGPT and SGOT (15 and 75 mg/kg) and alkaline phosphatase (75 mg/kg) were noted. Localized gastric necrosis was found in 2 dogs at the highest dose and a non-dose-dependent fatty degeneration of the liver, which varied from animal to animal, was also seen.

Inhalation (Oral)

A 6 month study in rats was performed using doses of 128, 256 and 384 mcg per rat per day. Measurements included ciliary beat frequency, lung mechanics and blood gas. The only finding was a dose related decrease in growth rate of the male animals.

A 6 month inhalation toxicity study was performed in rhesus monkeys utilizing daily doses of 20, 800 and 1600 mcg. All findings were negative including measurements of lung mechanics, ciliary beat frequency and blood gases.

Inhalation (aqueous nasal spray)

A 26-week nose-only inhalation study was performed in Sprague-Dawley rats (n=20/sex) using Ipratropium Bromide Nasal Spray 0.03, 0.06 or 0.12%. Daily exposure ranged from 126 mcg/kg to 2016 mcg/kg ipratropium bromide. There were 9 deaths in the highest dose group which were attributed to test substance administration. Reduced body weight gain, decreased food consumption and clinical signs of toxicity were also noted at this dose. Reduced body weight gain was also observed in males of the 504 mcg/kg/day group. A dose of 252 mcg/kg/day of ipratropium bromide was considered to be a Ano toxic effect level@ in this study, and a dose of 2016 mcg/kg/day approximated a “maximum tolerated dose”.

Thirteen week intranasal studies were performed in dogs, with Ipratropium Bromide Nasal Spray 0.03, 0.06 and 0.12%. The dose schedules were equivalent to 168, 336, 504, 1008 and 2016 mcg/day. There were no treatment-related effects on mortality, food consumption, body weight or clinical pathology. Microscopic evaluation of the nasal turbinates of the dogs treated at the higher dosages of Ipratropium Bromide Nasal Spray (504, 1008 and 2016 mcg/day) revealed some inflammatory lesions. However, the increased observation of these findings at 13 weeks versus 4 weeks in each group supported the hypothesis that these lesions were probably caused by the frequency of test material instillation rather than by irritation due to the drug.

A 26-week intranasal toxicity study was performed in beagle dogs (n=48) to determine the potential for three different formulations of Ipratropium Bromide Nasal Spray (0.03, 0.06 and 0.12%) to cause local and systemic toxicity when administered subchronically. There were 5 test groups including a vehicle control group; an applicator control group; Ipratropium Bromide Nasal Spray 0.03%, 50.4 mcg/kg/day; Ipratropium Bromide Nasal Spray 0.06%, 100.8 mcg/kg/day; and Ipratropium Bromide Nasal Spray 0.12%, 201.6 mcg/kg/day. There was no evidence of toxicological or histopathological effects in any treated animal in this study. There were also no treatment related effects on body weight gain, or ophthalmoscopic, electrocardiographic , nasal and clinical pathological examinations. Chronic inflammatory changes were noted in the nasal turbinates, larynx and lungs, but occurred with similar incidence and severity in all groups and were not considered to be drug related.

Mutagenicity

Three Ames tests, a micronucleus test in mice, a cytogenetic study in Chinese hamsters, and a dominant lethal test in mice were performed to assess the mutagenic potential of ipratropium bromide. Two positive tests (one Ames and the micronucleus study) were apparently spurious as they could not be reproduced with subsequent exhaustive experimentation. In the cytogenetic study, a dose

related increase in the number of chromatid gaps, but not of other aberrations, was seen. The significance of this finding is not known. All other test results were negative.

Carcinogenicity

Carcinogenicity studies in mice (107 weeks duration) and rats (114 weeks duration) utilizing oral doses of up to 6 mg/kg were performed. These studies demonstrated that ipratropium bromide does not have a tumorigenic or carcinogenic effect.

TERATOLOGY AND REPRODUCTION

Reproductive Studies

Three teratological studies, one in mice using oral doses of 2 and 10 mg/kg, and two in rats, were performed. The first study used the same doses and the second employed 10 and 20 mg/kg and revealed no drug induced fetal abnormalities.

A similar oral study in rabbits utilizing doses of 2 and 10 mg/kg again showed no teratogenic or embryotoxic effects of ipratropium bromide.

An inhalation teratology study in rabbits using doses of 0.3, 0.9 and 1.8 mg/kg demonstrated no effect on litter parameters, and no embryotoxic and teratogenic effects.

A fertility study in rats with oral doses of 5, 50 and 500 mg/kg being given 60 days prior to and during early gestation was performed. Fertility was delayed in 8 of 20 couples at 500 mg/kg and spurious pregnancy in 5 of 20 females occurred at this dose. In addition, the conception rate was decreased in 75% of females at this dose. No embryotoxic or teratogenic effects were observed.

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